

Current landscape and future directions of therapeutic approaches for adenoid cystic carcinoma of the salivary glands (Review)

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Abstract. Adenoid cystic carcinoma (ACC) of the salivary glands is the second most common type of salivary gland cancer, and is characterized by a poor prognosis and an unclear pathology. The incidence of ACC is rare, as it accounts for 10-15% of all salivary gland tumors and affects mainly patients aged between 50 and 60 years. The annual incidence rate is estimated to be ~4.5 cases per 100,000 individuals. Due to its rarity and the use of contaminated cell lines in previous investigations, the precise etiological factors underlying ACC remain poorly understood. Current treatment modalities, typically involving surgery with or without postoperative radiotherapy, often prove unsatisfactory due to the potential for local recurrence and delayed distant metastases, which may manifest 3-5 years after treatment and constitute the primary failure of existing therapeutic approaches. The indolent growth pattern, along with perineural and perivascular invasion, is potentially responsible for the delayed onset of metastases. No effective systemic therapy has been established so far. Therefore, the management of ACC represents a significant

therapeutic challenge. Exploring the molecular characteristics of ACC, including the reasons behind its propensity for perineural invasion and its potential correlation with the immune system, offers promising strategies for managing ACC and could open up novel pathways for future therapeutic interventions. Currently, the use of immunotherapy in ACC treatment has shown limited effectiveness. While the exact mechanism underlying the lack of response to immunotherapy in ACC remains unknown, the low levels of tumor-infiltrating lymphocytes in these tumors may contribute to this resistance. Therefore, identifying novel targets to enhance the immune response against tumor cells is essential. The present review provides an update on clinical studies and explores novel therapeutic targets that could be effective in the therapeutic management of ACC.

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1. Introduction

Adenoid cystic carcinoma (ACC) is a rare malignancy that arises from cells within the salivary glands, although its precise cellular origin remains unclear (1). ACC comprises ~1% of all types of head and neck cancer, positioning itself as the second most common salivary gland cancer after mucoepidermoid carcinoma (2). ACC predominantly arises in the minor salivary glands, a location which accounts for >50% of all ACC cases, and is primarily localized within the oral cavity, hard palate, throat mucosa or paranasal sinuses (3). While the salivary glands are the most common site for ACC, this type of cancer can also arise in other locations, such as the breast, lungs or the Bartholin glands. ACC is particularly rare in the breast, accounting for <1% of all breast cancer cases (4). Unlike the salivary gland subtype, breast ACC, while slow growing, generally has a favorable prognosis (4). Pulmonary ACC, by

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Abbreviations: ACC, adenoid cystic carcinoma; CSC, cancer stem cell; CDK, cyclin-dependent kinase; CXCR4, C-X-C chemokine receptor type 4; CTLA-4, cytotoxic T cell antigen 4; EGFR, epidermal growth factor receptor; IGFR-1, insulin-like growth factor; mTOR, mammalian target of rapamycin; PDX, patient-derived xenograft; PI3K, phosphatidylinositol 3-kinase; PSMA, prostate-specific membrane antigen; PRMT5, protein arginine methyltransferase 5; PD-1, programmed death receptor 1; PCZ, prochlorperazine; PNI, perineural invasion; SCC, squamous cell carcinoma; TRKA, tropomyosin receptor A; VEGF, vascular endothelial growth factor

Key words: ACC, radiotherapy, surgery, distant metastases, local recurrence, PNI

contrast, shares few similarities with its salivary counterpart. Although the histological patterns of these tumors are similar, perineural invasion is notably less common in pulmonary ACC compared to salivary ACC. Additionally, pulmonary ACC has a slightly better prognosis (5). Surgical resection remains the treatment of choice for pulmonary ACC, as no effective systemic therapy is currently established (5). Due to its non-specific clinical presentation, ACC in the Bartholin glands often goes unnoticed and is therefore frequently diagnosed at an advanced stage (6). ACC exhibits a propensity for perineural invasion and distant metastases, which may manifest years after initial treatment (7). Surgery followed by radiotherapy remains the cornerstone of ACC treatment (8). Due to the use of contaminated cell lines in numerous previous research studies (9,10) further investigation is needed to elucidate the pathogenesis of ACC and identify potential therapeutic targets (11). The ACC2, ACC3 and ACCM cell lines were primarily contaminated with cervical cancer cells, while the ACCS cell line was composed of T24 urinary bladder cancer cells (11).

Several recently published papers (12-14) have provided new insights into potential therapeutic targets for managing ACC. In the present review, a comprehensive literature search of publications from January 2019 to April 2024 in the PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) and Cochrane Library (<https://www.cochranelibrary.com>) databases was conducted. Case reports were excluded from the analysis. The primary aim of the present review was to elucidate advancements in the treatment of ACC, while also highlighting potential pathways for therapeutic interventions in patients with ACC. Articles focusing on therapeutic modalities were selected, with particular emphasis on novel possible therapies validated by randomized controlled trials.

Epidemiology. Current data suggests that ACC occurs more frequently in females, with a distribution of 60% in females compared with 40% in males (15). The overall incidence of ACC accounts for ~4.5 cases per 100,000 individuals (16), representing ~1% of all types of head and neck cancer and ~10% of all salivary gland tumors (17). ACC, originating from the mucous glands, can occur in various body sites beyond the salivary glands (18). A large proportion of the available literature indicates that minor salivary glands represent the most common site for ACC, accounting for >50% of cases. The palate is the most frequently affected location, although ACC can also develop in the tongue, paranasal sinuses, nasopharynx, larynx and lacrimal glands (19,20). Among the major salivary glands, the parotid gland is the most prevalent site for ACC (21). Additionally, ACC may arise in the breast, tracheo-bronchial tree, lungs, prostate, esophagus, skin, Bartholin glands and cervix (22). Although this malignancy can occur at any age, it is most commonly diagnosed in patients between 50 and 60 years of age (23).

Etiology. Due to the rarity of ACC, the precise etiology and pathogenesis remain poorly understood (24). While smoking and alcohol intake are known risk factors for other types of cancer in the head and neck area, especially squamous cell carcinoma, they have not been confirmed as risk factors for ACC (25). Several genetic and chromosomal alterations, including TP53,

NOTCH1, NOTCH2 or loss of the CDKN2A/CDKN2B locus, may be involved in ACC pathogenesis, with a recurrent t(6;9) (q23;p23) translocation resulting in a fusion between the MYB proto-oncogene, transcription factor (MYB) and nuclear factor I/B (NFIB) genes, considered to be a genetic hallmark of ACC (26). Nonetheless, the exact causes of ACC, including potential risk factors, require additional research.

Clinical presentation and diagnosis. The symptoms of ACC can vary depending on the location of the tumor (27), with a lack of symptoms reported if the tumor is located in the paranasal sinuses or dysphagia if it is located on the hard palate, the base of the tongue or the throat mucosa (28). Dyspnea, coughing, hoarseness or wheezing may occur if the minor salivary glands of the upper aerodigestive tract are involved (29). In advanced stages of the disease, dull pain and altered sensation of the tongue, palate or face may occur, which are manifestations of perineural invasion (PNI) of the local nerves, a characteristic phenomenon of ACC (30). PNI is relatively common, affecting ~43.2% of cases and is considered an independent factor for a poor prognosis (31). Despite its slow development, ACC is considered an aggressive tumor that can readily invade the surrounding tissues. Other factors that can influence the risk of distant metastases include a solid histology, a tumor size >3 cm and the involvement of loco-regional lymph nodes (32). Distant metastases are not uncommon and tend to spread via the perivascular route, typically affecting the lungs, followed by the bones and liver (33). As a result, local recurrences (60%) and distant metastases (40%) are frequent, and can occur even decades after definitive treatment (34). The 5-year overall survival rate ranges from 55 to 70%, which is higher compared with that of other sinonasal malignancies, but the overall survival rate drops to 40% at 10 years and further to 15% at 20 years after diagnosis. Therefore, extended follow-up for at least 15 years, if not lifelong follow-up, is necessary (35). Distinguishing salivary ACC from other malignant salivary tumors requires advanced pathological skills. ACC shares histopathological features with other salivary gland tumors, such as polymorphous adenocarcinoma and basal cell adenocarcinoma (27). The cribriform, tubular and solid growth patterns observed in ACC can occasionally resemble other malignancies, including pleomorphic adenoma or polymorphous low-grade adenocarcinoma, leading to diagnostic confusion (36). While the classic cribriform pattern is often recognizable, the tubular and solid variants can be more difficult to distinguish from other salivary gland tumors, particularly when these patterns dominate the tumor (36). Therefore, the role of expert pathological review in the diagnosis of salivary ACC is crucial due to the propensity of the tumor for late local recurrence and distant metastasis. In such cases, experienced pathologists could accurately evaluate biopsy samples to confirm the presence of recurrent or metastatic ACC and distinguish it from other possible malignancies or benign conditions. Expert pathological review would serve as a quality assurance measure, and provide a second opinion to confirm initial diagnoses and prevent diagnostic errors. The role of molecular diagnostics in salivary ACC diagnosis is also critical for distinguishing the tumor from other salivary gland tumors. Specifically, the MYB-NFIB gene fusion, a molecular hallmark of ACC, aids in differentiating it from other tumors,

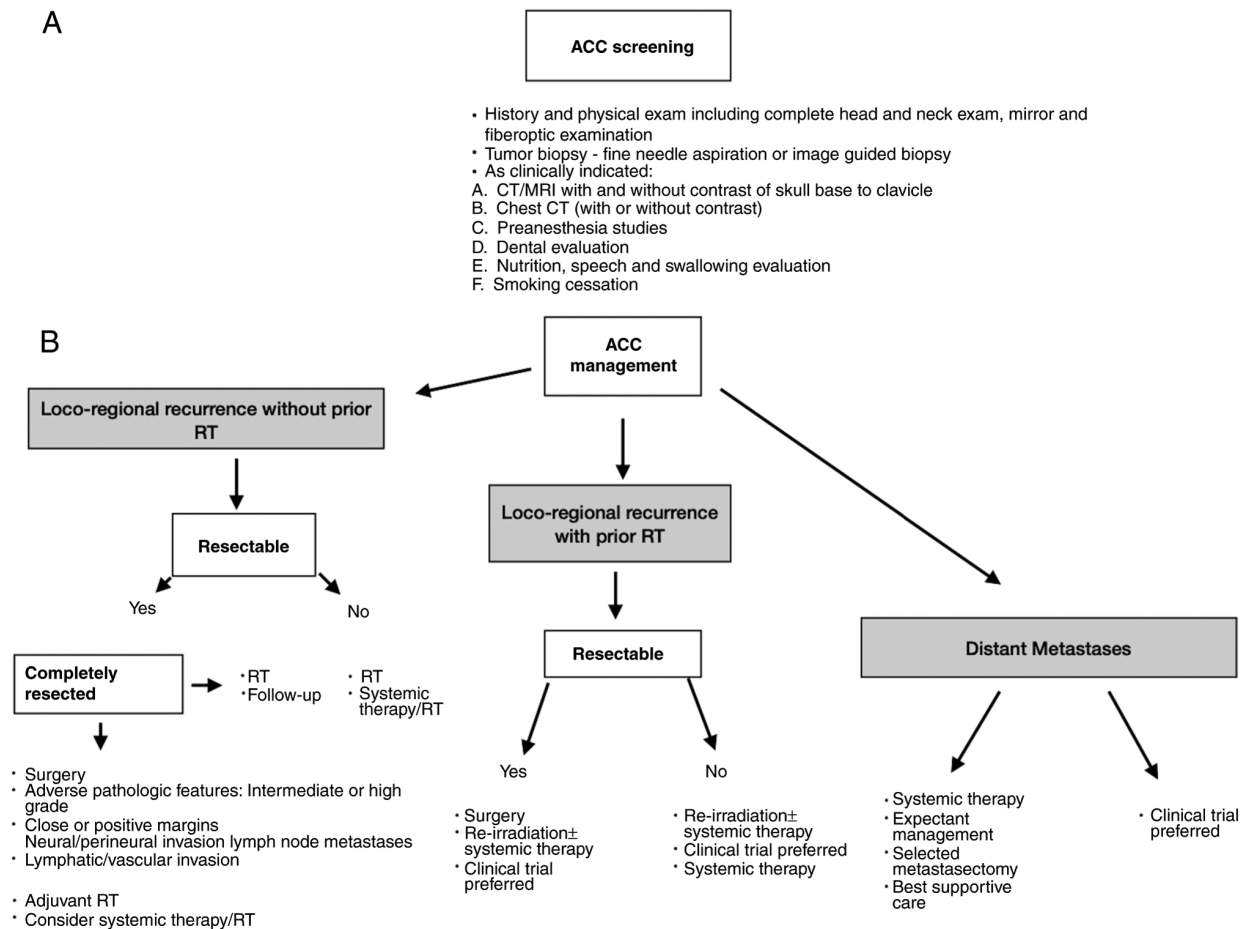


Figure 1. Schematic representation of (A) the screening process and (B) therapeutic strategies for addressing recurrence and metastasis in adenoid cystic carcinoma (ACC), as outlined by the National Comprehensive Cancer Network (NCCN) guidelines. ACC, adenoid cystic carcinoma; RT, radiotherapy.

such as Warthin's tumor (37). Additionally, while immuno-histochemical staining can assist in the diagnosis, markers such as S-100, CK-7, CK-17 or SOX10 are not entirely specific to ACC and may overlap with those of other salivary gland tumors. Therefore, careful interpretation of staining patterns in conjunction with histological findings, is essential. The definitive diagnosis of salivary ACC remains challenging due to the histological diversity of types of salivary gland cancer. This complexity is underscored by the 2022 World Health Organization classification of salivary gland tumors, which introduces new malignant entities such as microsecretory carcinoma and sclerosing microcystic adenocarcinoma (38).

Clinical management. Current treatment options for ACC typically involve surgical resection followed by postoperative radiotherapy, which appears to be a feasible approach for achieving locoregional control in early stage disease (39). In a study by Ishida *et al* (40), which involved 58 cases of ACC treated solely with surgical excision, the 10-, 20- and 25-year survival rates were 63.7, 27.3 and 20%, respectively. Although surgery remains the preferred therapeutic option for patients with ACC, it often presents significant challenges due to the tumor's location, particularly when it arises from the minor salivary glands in areas such as the paranasal sinuses. Radical resection can be difficult to achieve, which underscores the need for postoperative radiotherapy to compensate for

incomplete tumor removal (41). It was previously reported that patients with ACC who did not receive postoperative radiotherapy were >13 times more likely to experience local recurrence (42). Nevertheless, radiotherapy alone is seldom used and is usually dedicated for patients with advanced or recurrent disease (Fig. 1) (43). The frequent incidence of local recurrence and distant metastasis, even years after completion of treatment, highlights the ineffectiveness of these therapies. Furthermore, neither the National Comprehensive Cancer Network (NCCN) (8) nor the American Society of Clinical Oncology (44) provides specific guidelines for effective chemotherapeutic regimens in the management of ACC. In palliative cases, chemotherapeutic regimens typically include cisplatin and 5-fluorouracil, or combination therapies such as cisplatin, doxorubicin and cyclophosphamide (CAP) (45). However, in the use of monotherapy, agents such as cisplatin, mitoxantrone, epirubicin, vinorelbine, paclitaxel and gemcitabine may be employed (46). Nevertheless, the effectiveness of these chemotherapeutics remains limited, since these drugs are reported to have no or only slight effects on the prognosis of the patient (46). According to data from the available literature, the response rate for CAP is estimated to be between 18 and 31% (47). In a phase II study involving cisplatin and docetaxel, which predominantly included patients with ACC, as well as other types of salivary gland cancer, the median duration of response was 6.8 months. The median progression-free

survival time was 9.4 months and the overall survival time was ~28.2 months (48). Nevertheless, the data confirmed that chemotherapy has limited effectiveness in treating ACC and is primarily used as a palliative approach.

2. Current and novel therapies

Therapeutic management of ACC. Currently, there is no effective systemic therapy for managing ACC of the salivary glands, particularly in advanced stages or for inoperable tumors. This emphasizes the need to explore new treatment strategies, especially those incorporating targeted therapies, to improve the management of late-stage ACC. Although no new systemic therapies for managing ACC have recently been approved, the primary goal of this review is to outline the current therapeutic targets and describe ongoing clinical trials (Table I) that are exploring potential treatment options for ACC, while also providing data on concluded clinical trials (Table II).

Database search strategy and selection criteria. An extensive literature search was conducted using the PubMed and Cochrane Library databases. The search strategy utilized combined Medical Subject Headings terms and key words, including: 'adenoid cystic carcinoma of a salivary gland' or 'ACC', 'salivary adenoid cystic carcinoma', and 'SACC'. There were no restrictions on language, geographical region, patient age or follow-up duration. Prospective or retrospective clinical and animal studies were included in the present review. The exclusion criteria were as follows: Editorials, letters, reviews, case reports, lack of relevant outcome reporting and duplicate publications.

Vascular endothelial growth factor (VEGF). The high expression of VEGF in over two-thirds of patients with ACC has been identified as a potentially promising therapeutic target (49). Molecular studies on ACC have also shown that high MYB expression levels are correlated with increased VEGF expression levels (50-52). Despite this correlation, preclinical studies using the VEGF inhibitor regorafenib, which showed successful results by inhibiting ACC cell migration and intravascular cancer migration, did not translate into clinical benefit for patients with ACC in human trials (53). Similar unsuccessful outcomes were observed in studies assessing the effectiveness of sunitinib or nintedanib in patients with ACC (54,55). However, lenvatinib and axitinib showed relatively higher objective response rates, with 11-16 and 9-17%, respectively (56). In a phase II clinical trial with axitinib and avelumab in patients with recurrent disease, the partial response was confirmed in 28 out of 40 enrolled patients, with a median overall survival time estimated at 16.6 months. However, the aforementioned study reached its primary endpoint with 4 partial responses in 28 evaluable patients (57,58). Another study conducted on lenvatinib use among patients with recurrent or metastatic ACC demonstrated a partial response in 5 patients only among the 33 enrolled and 32 evaluable for the primary endpoint. A large proportion of patients (24) had stable disease; however, the severe side effects, including hypertension or oral pain, resulted in treatment discontinuation (59). Locati *et al* (60) evaluated lenvatinib in patients with recurrent or metastatic ACC and found only three partial

responses among 26 participants, with a median overall survival time of 27 months, a median progression-free survival time of 9.1 months and a median duration of response of 3.1 months. In another study assessing the impact of VEGFR2 inhibition in recurrent or metastatic ACC, rivocecanib demonstrated limited effectiveness in 72 evaluated patients, with an overall response rate of 15.3%, a median duration of response of 14.9 months and a median progression-free survival time of 9.0 months (61). A clinical trial evaluating the effectiveness of cabozantinib among patients with salivary gland cancer, including ACC, reported high levels of toxicity and was closed prematurely (59). Additionally, in another study, only 1 out of 15 patients with ACC achieved a partial response, which was comparable to the response rates observed in other types of salivary gland cancer (62). Thus, even though VEGFR is highly expressed in ACC tissue, it does not appear to be an effective therapeutic target.

Epidermal growth factor receptor (EGFR). EGFR has been found to be overexpressed in >85% of ACC cases (63). However, therapies targeting EGFR inhibition have shown limited effectiveness in managing ACC. The EGFR monoclonal antibodies act by inhibition of phosphorylation and cellular signaling, and support tumor clearance through antibody-dependent cellular cytotoxicity (ADCC) (64). Previous studies on cetuximab, gefitinib and lapatinib inhibiting both EGFR and HER2 did not change the disease course substantially in patients with ACC (15,65). In a study by Bossi *et al* (66), cetuximab contributed to disease stabilization for >6 months. Despite the increased expression levels of EGFR in ACC, studies investigating EGFR inhibition have shown no objective responses (67-69). Nevertheless, in a study conducted by Chew *et al* (70), the co-administration of prochlorperazine (PCZ) with an EGFR inhibitor was investigated as a way to enhance the availability of surface EGFR for antibody binding, thereby improving ADCC. The inhibition of dynamin by PCZ and clathrin-mediated endocytosis allows for increased EGFR expression on the surface of cancer cells, potentially leading to enhanced ADCC and an improved response in patients with recurrent or metastatic ACC (71).

Fibroblast growth factor receptor 1 (FGFR1). The increased expression of FGFR1 in ACC contributed to research on the potential FGFR1 inhibitors, which may decrease cancer cell proliferation (72). In an experimental animal model of ACC, use of dovitinib, a multi-kinase inhibitor, resulted in slowed disease progression (73). These findings were subsequently validated in a study on dovitinib in patients with ACC conducted by Dillon *et al* (74), which observed a partial response in 2 patients and disease stabilization in 65% of included patients (71). Despite achieving disease stabilization, 67% of the patients eventually experienced cancer progression, with an overall median progression-free survival of 8.5 months. However, given that dovitinib does not act as a selective kinase inhibitor, it remains unclear whether the observed response in the patients was due to FGFR1 inhibition or other targeted kinases, including KIT, PDGFR, RET, CSF1-R, TrkA and FLT3. An alternative agent, lenvatinib, that inhibits not only FGFR 1-3, but also VEGFR2, KIT proto-oncogene receptor tyrosine kinase (c-KIT), ret proto-oncogene (RET) and

Table I. List of clinical trials evaluating agents for adenoid cystic carcinoma treatment.

Clinical trial no.	Drug name	Drug target	Phase	No. of cases	Primary endpoint	Estimated study completion date
NCT04974866	EGFR-TKIs	EGFR-TKI	II	20	ORR by RECIST	2026-07-31
NCT06118086	REM-422	MYB mRNA degrader	I	65	ORR by RECIST	2026-06-01
NCT04973683	AL-107	NOTCH inhibition	I	14	ORR by RECIST	2024-12-15
NCT05774899	CB-103 with either lenvatinib or abemaciclib	CB-103, an oral NOTCH pathway, inhibitor; abemaciclib a CDK4/6 inhibitor; lenvatinib, a VEGFR TKI	I/II	34	ORR by RECIST	2026-06-01
NCT06322576	177Lu-PSMA	Human PSMA-targeting ligand, conjugated to the β -emitting radioisotope 177Lu	II	10	ORR by RECIST	2035-12
NCT02780310	Lenvatinib	TKI	II	33	ORR by RECIST	2025-05
NCT02098538	Regorafenib	TKI	II	38	ORR by RECIST	2025-03
NCT06199453	177Lu vipivotide tetraxetan	Human PSMA-targeting ligand, conjugated to the β -emitting radioisotope 177Lu	II	32	ORR by RECIST	2027-11
NCT05074940	Amivantamab	EGFR-MET bispecific antibody	II	18	ORR by RECIST	2028-08-05
NCT04209660	Lenvatinib and pembrolizumab	VEGFR inhibitor and programmed death receptor 1 inhibitor	II	64	ORR by RECIST	2024-12
NCT05930951	OBT076 with or without balstilimab targeting PD1	CD205/Ly75-directed antibody-drug conjugate-targeting the CD205/Ly75 molecule, also known as DEC-205 (Dendritic and Epithelial Cell-205).	I	32	ORR by RECIST	2027-09
NCT03146650	Nivolumab and ipilimumab	Nivolumab, programmed death-ligand 1; ipilimumab, cytotoxic T cell antigen 4	II	25	ORR by RECIST	2025-08-11
NCT05010629	9-ING-41 with carboplatin	9-ING-41, a GSK-3 β inhibitor; carboplatin chemotherapy	II	35	ORR by RECIST	2025-08-30
NCT05194072	SGN-B7H4V	B7-H4	I	430	ORR by RECIST	2027-01-31
NCT03556228	VMD-928	Tropomyosin receptor A inhibitor	I	74	ORR by RECIST	2025-12
NCT04140526	ONC-392 and pembrolizumab	Humanized anti-CTLA4 IgG1 monoclonal antibody	I/II	914	ORR by RECIST	2024-12-31
NCT04249947	P-PSMA-101 CAR-T cells and rimiducid acting as rapamycin analog	P-PSMA-101 CAR-T cells	I	60	ORR by RECIST	2036-09

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; 177Lu, lutetium Lu 177; MYB, MYB proto-oncogene, transcription factor; PSMA, prostate-specific membrane antigen; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

platelet EGFRa and b, is considered a more potent therapeutic option (71). A study by Tchekmedyan *et al* (59) investigating lenvatinib use confirmed a partial response in 32 patients

with recurrent or metastatic ACC, with 8 patients showing >20% reduction in tumor size. Both studies on lenvatinib and dovitinib required dosage modifications due to adverse effects

Table II. List of clinical trials with published results.

Drug	No. of cases	Biological target	Primary endpoint	Trial result	Clinical trial no.	URL
Regorafenib	38	VEGFR1, VEGFR2, VEGFR3, KIT, RET, BRAF and FGFR1	PFS, ≥ 6 months ORR (CR and PR) for 6 months	Not reported	NCT02098538	https://clinicaltrials.gov/ct2/show/NCT02098538 .
Vorinostat	30	HDAC	ORR, up to 6 months	- PR, 1 patient (3%) with response duration of ≥ 11.2 months. - SD, 25 patients (83%). - Median PFS, 12.7 months. - PFS > 1 year, 6 patients (20%). - Median OS, not reached.	NCT01175980	https://clinicaltrials.gov/ct2/show/NCT01175980
Sorafenib	23	Serine/threonine kinases c-Raf/b-Raf, VEGFR2, VEGFR3, PDGFR- β , FMS-like tyrosine kinase 3, c-kit and p38 α	PFS, 12 months Secondary endpoints: ORR, OS and toxicity	- PFS at 12 months, 46.2%. - Median PFS, 11.3 months. - Median OS, 19.6 months. - PR, 2 of 19 patients (11%). - SD, 13 of 19 patients (68%). - PD, 4 of 19 patients (21%). - No ORR. - SD, 20 of 23 patients (87%).	Eudra CT2008-000066-22	https://ichgcp.net/eu-clinical-trials-registry/trial/2008-000066-22/results
Cetuximab	23	EGFR	CR, PR and SD	Not reported.	NCT01192087	https://clinicaltrials.gov/study/NCT00509002 https://clinicaltrials.gov/study/NCT01192087?cond=NCT01192087&rank=1
Cetuximab + intensity modulated radiation therapy	49	EGFR	Toxicity of the combined therapy composed of RT + cetuximab Secondary endpoints: ORR, PFS and OS	Not reported.		
Cetuximab + RT + cisplatin or Cetuximab + cisplatin and 5-FU	21	EGFR	PFS Secondary outcomes: ORR, OS	- For locally advanced ACC (n=9): Median PFS, 64 months; CR, 2 (22%); 2 PR (22%); 5 SD (55.6%); no PD (0%); and OS was not reached. - For metastatic ACC (n=12): Median PFS, 13 months; maximum PFS, 48 months; 5 PR (42%); 7 SD (58%); no PD (0%); and OS, 24 months.	EudraCT 2006-001694-23	https://www.clinicaltrialsregister.eu/ctr-search/search?query=2006-001694-23
Dovitinib	20	VEGFR1, VEGFR2, VEGFR3, FGFR1, FGFR2, FGFR3 and PDGFR- β	ORR and SD rate	Not reported	NCT01678105	https://clinicaltrials.gov/study/NCT01678105?cond=NCT01678105&rank=1

Table II. Continued.

Drug	No. of cases	Biological target	Primary endpoint	Trial result	Clinical trial no.	URL
Dovitinib	21	VEGFR1, VEGFR2, VEGFR3, FGFR1, FGFR2, FGFR3 and PDGFR- β	ORR	- PR, 2 of 19 evaluable patients (10.5%). - SD >6 months, 9 patients (43%). - Total SD, 15 (71%). - 6 patients with shorter follow-up did not show progression. - 4 patients (19%) progressed early <4 months.	NCT01524692	https://clinicaltrials.gov/study/NCT01524692?cond=NCT01524692&rank=1
Axitinib	33	VEGFR1, VEGFR2, VEGFR3 and c-kit	ORR	- PR, 3 of 33 patients (9%). - SD, 25 patients (76%). - SD $\geq$6 months, 11 patients (33%) - Bortezomib only: No objective response; SD, 15 of 21 evaluable patients (71%); median PFS, 6.4 months; and OS 21 months. - Doxorubicin added: PR, 1 of 10 evaluable patients (10%); and SD, 6 (60%).	NCT01558661	https://clinicaltrials.gov/study/NCT01558661?cond=NCT01558661&rank=1
Bortezomib + doxorubicin	24	26S proteasome, NF- κ B	ORR	- Bortezomib only: No objective response; SD, 15 of 21 evaluable patients (71%); median PFS, 6.4 months; and OS 21 months. - Doxorubicin added: PR, 1 of 10 evaluable patients (10%); and SD, 6 (60%).	NCT00077428	https://clinicaltrials.gov/study/NCT00077428?cond=NCT00077428&rank=1
Bortezomib + doxorubicin	10	26S proteasome, NF- κ B	ORR and SD rate	Not reported	NCT00581360	https://clinicaltrials.gov/study/NCT00581360?cond=NCT00581360&rank=1
Nelfinavir	15	MAPK, PI3K/Akt signaling pathway	PFS and ORR	- No objective responses. - SD, 7 patients (47%). - SD $\geq$6 months, 2 (13%). - PD, 9 of 12 assessable patients (75%). - Median PFS, 5.5 months.	NCT01065844	https://clinicaltrials.gov/study/NCT01065844?cond=NCT01065844&rank=1
Sunitinib	14	VEGFR1, VEGFR2, VEGFR3, c-kit, PDGFR- α , PDGFR- β , RET and FLT3	ORR	- No objective responses. - SD, 11 patients (79%). - PD, 2 patients (14%). - Median OS, 18.7 months. - Median time to progression, 7.2 months.	NCT00886132	https://clinicaltrials.gov/study/NCT00886132?cond=NCT00886132&rank=1
MK 2206	19	AKT	ORR	Not reported	NCT01604772	https://clinicaltrials.gov/study/NCT01604772?cond=NCT01604772&rank=1
Imatinib	10	c-kit	ORR	- No objective responses. - SD, 2 (20%) for $\geq$6 months.		

Table II. Continued.

Drug	No. of cases	Biological target	Primary endpoint	Trial result	Clinical trial no.	URL
Dasatinib	40 ⁺	c-kit	ORR, PFS	- No objective responses. - PR, 0 patients (0%). - SD, 21 patients (52%). - Median PFS, 4.8 months.	NCT00859937	https://clinicaltrials.gov/study/NCT00859937
Lapatinib	19 ⁺	EGFR, erbB2(HER2)	ORR	- No objective responses. - SD, 15 patients (79%). - SD for ≥6 months, 9 patients (47%).	NCT00095563	https://clinicaltrials.gov/study/NCT00095563
Gefitinib	18 ⁺	EGFR	ORR	- No objective responses. - SD ≥9 months, 7 patients (38%). - Median PFS, 4.3 months. - Median OS, 25.9 months.		https://ichgcp.net/clinical-trials-registry/NCT00509002
Everolimus	34	mTOR	PFS rate at 4 months. Secondary endpoint: ORR	- 4-month PFS probability, 65.5% - No objective responses. - SD, 27 patients (79%). - SD ≥6 months, 13 patients (38%).	NCT01152840	https://ichgcp.net/clinical-trials-registry/NCT01192087

ACC, adenoid cystic carcinoma; ORR, objective response rate; PFS, progression-free survival; PR, partial response; SD, stable disease; OS, overall survival; PD, progressive disease; CR, complete response; RT, radiotherapy.

such as hypertension, anemia or diarrhea (59,71). Lenvatinib has received a category 2B recommendation for patients with progressive, recurrent or metastatic ACC in the NCCN guidelines (8). A clinical trial combining lenvatinib and pembrolizumab did not show an improved overall response rate compared with lenvatinib alone in patients with ACC. A complete response rate was found in only 1 out of 17 patients, with 13 patients achieving stable disease (75). Another study evaluating the effectiveness of the FGFR1 inhibitor AZD4547 in treating ACC of the lacrimal gland found that adding cisplatin led to lower cell proliferation and migration compared with the control group treated with cisplatin alone (76).

c-KIT. Although receptor tyrosine kinase c-KIT is upregulated in 65-90% of ACC tumors (77), clinical trials involving imatinib, a c-KIT inhibitor, demonstrated that the drug was largely ineffective in treating salivary gland ACC (78). While imatinib has been successful in treating gastrointestinal stromal tumors and chronic myeloid leukemia (79), in one study examining its use in ACC, only 2 out of 42 patients experienced an objective tumor response (80). Similarly, dasatinib failed to show any improvement in patients with recurrent or metastatic ACC (81). Furthermore, the combination of cisplatin with imatinib did not result in any significant improvement in response rates, as only 3 patients (10%) exhibited a partial response (82). Thus, despite the high expression of c-KIT in salivary gland ACC, the protein does not appear to play a significant role in the pathogenesis of this tumor type, rendering it an unattractive target for future therapeutic interventions.

MYB. The translocation t(6;9)(q22-23;p23-24), which leads to the fusion of the MYB proto-oncogene with the NFIB transcription factor gene, is a hallmark of ACC, as it is detected in ~50% of cases (83). However, the precise frequency of MYB-NFIB fusions in ACC remains unknown, as it varies depending on the method of detection used (for example, fluorescence *in situ* hybridization vs. PCR/RNA-seq) and the type of material analyzed (for example, fresh-frozen vs. formalin-fixed paraffin-embedded tissue) (84). MYB protein expression by IHC was recently demonstrated in >90% of ACCs in a large multi-institutional study (85). Moreover, MYB gene upregulation itself serves a key role in the cancer pathogenesis, as it promotes tumorigenesis by enhancing cancer stemness; however, MYB was previously thought to present a difficult therapeutic target due to its nature as a transcription factor (86). Nevertheless, the current and past studies proved that MYB inhibition has had a beneficial effect on patients with ACC. The approach to MYB inhibition may be accomplished by direct MYC degradation or by the inhibition of MYB-associated proteins (87). A study by Yusenko *et al* (88) confirmed that use of polyether ionophore monensin A results in the inhibition of MYB and leads to its degradation *in vitro*. All-trans retinoic acid (ATRA) also has an inhibitory effect on the MYB gene in ACC cells (89). Another molecule inhibiting MYB-NFIB fusion is insulin-like growth factor receptor 1 (IGFR1) (90). IGFR1, similar to EGFR, stimulates ACC proliferation as the MYB-NFIB fusion in ACC is regulated by IGFR1 through an autocrine loop (90). In ACC models, linstinib targeting IGFR1, crizotinib targeting ALK or gefitinib

targeting EGFR resulted in tumor growth reduction (91). In a clinical trial evaluating figitumab combined with dacomitinib, and another trial assessing R1507 with sorafenib, the response rate was observed in 1 patient, while stable disease was seen in 3 patients (92,93). However, due to the development of MYB-targeted inhibitors, MYB is becoming an increasingly attractive therapeutic target. In a study conducted by Yusenko *et al* (94), a Bcr-TMP MYB-inhibitory particle resulted in significantly decreased ACC cell proliferation.

NOTCH. The NOTCH signaling pathway serves a pivotal role in numerous cellular processes that are crucial for cell differentiation, but it has also been implicated in the pathogenesis of several types of cancer, including ACC (95). Although NOTCH1 mutations are less common compared with MYB gene alterations, they are typically found in ~15% of ACC cases (96). Furthermore, studies suggest that NOTCH mutations in patients with ACC are associated with a poorer prognosis (97). Given the role of NOTCH signaling in regulating tumor cell behavior, acting as both an oncogene and a tumor suppressor depending on the cellular and tissue context, NOTCH inhibitors are an appealing therapeutic strategy for certain subsets of ACC. Several preclinical studies have confirmed the effectiveness of NOTCH1 inhibitors in ACC patient-derived xenograft (PDX) models (98). A previous study examined AL101 (osugacestat), a potent γ -secretase inhibitor that prevents the activation of all four NOTCH receptors (99). The antitumor activity of AL101 was demonstrated in ACC cell lines, organoids and PDX models (99). Notably, AL101 showed strong antitumor effects in both *in vitro* and *in vivo* models of ACC with activating NOTCH1 mutations that constitutively upregulated NOTCH signaling pathways (99). This provides a rationale for further clinical trials evaluating AL101 in patients with NOTCH-driven relapsed or refractory ACC. In a phase II clinical trial assessing AL101, 9 out of 77 patients experienced a partial response, while 44 had stable disease (99). In a phase I study of the pan-NOTCH inhibitor CB-103 for patients with ACC and other tumors, no partial response was observed, but 23 out of 40 patients with ACC had stable disease, with a median progression-free survival time of 2.5 months and a median overall survival time of 18.4 months (100). A study of crenigacestat another pan-NOTCH inhibitor, demonstrated that only 1 out of 22 patients with ACC had a partial response, while 15 experienced stable disease (101). Another trial testing brontictuzumab targeting Notch1 receptor, showed favorable effects, with 2 out of 12 patients achieving a partial response and 3 achieving stable disease (102).

p53. Although p53 can be considered one of the most notable genes with mutations commonly found in numerous types of cancer, its incidence in ACC is less common, accounting for 10-20% of cases (103). However, in a previous study, increased p53 expression was observed in ~90% of ACC cases, indicating that it might serve as a potential therapeutic target (104). In the ACC PDX model, inhibiting the interaction between murine double minute 2 (MDM2) and p53 using MI-733 led to apoptosis, tumor regression and the prevention of tumor recurrence (105). Following this, a clinical trial is currently underway, assessing the efficacy of blocking MDM2-p53 with alrizomadlin (APG-115), with or without platinum-based

therapy, in salivary gland cancer, including ACC, with results yet to be published (106).

Phosphatidylinositol 3-kinase (PI3K)/phosphatase and tensin homolog (PTEN)/mammalian target of rapamycin (mTOR) pathway. PI3K activates AKT by phosphorylation and via certain transcriptional factors, including mTOR (107). In a study by Yu *et al* (108), proteins such as p-S6, p-STAT3, PAI, EGFR and hypoxia induced factor-1 α were significantly elevated in ACC samples compared with those in benign salivary lesions, such as pleomorphic adenoma and normal salivary glands. Similarly, a study by Liu *et al* (109) demonstrated decreased expression levels of PTEN in ACC samples, particularly in the solid subtype, compared with other salivary gland malignancies. Given that PTEN functions as a tumor suppressor, its reduced expression levels in ACC tissue might present a potential therapeutic target. In a phase II clinical trial involving everolimus, an mTOR inhibitor, among patients with ACC showing disease progression, treatment with everolimus resulted in a median progression-free survival time of 11.2 months. Of the 34 participants included, 15 showed tumor shrinkage and 27 exhibited stable disease (110). Additionally, a separate phase I study investigating the combination of everolimus with lenalidomide found that this regimen was safe and well tolerated, indicating a potential combination therapy for ACC (111).

Immune checkpoint inhibitors. Immunotherapy has transformed the treatment landscape for numerous types of cancer that previously had a poor prognosis. It is now a primary treatment option for several malignancies and is considered to be promising approach in cancer therapy (112–114). The expression levels of proteins such as cytotoxic T cell antigen 4 (CTLA-4), programmed death receptor 1 (PD-1) and programmed death-ligand 1 (PD-L1), which are primary targets for immunotherapeutic treatments, is significantly low in the environment of ACC (115). As ACC is considered to be a ‘cold tumor’, the lymphocytic infiltration in its microenvironment is sparse (116). Therefore, both past and ongoing research on the use of immunotherapy in ACC has yielded unsatisfactory results (15,117). The NISCAHN trial examined the efficacy of nivolumab, a PD-1 inhibitor, in 45 patients with recurrent or metastatic ACC. The results showed an overall response rate of only 0.8%, with a progression-free survival time of 6 months for 33% of patients (118). Another study of ACC patients, where nivolumab was combined with the CTLA-4 inhibitor ipilimumab, reported an even lower overall response rate compared with nivolumab alone, at ~6% (119). Additionally, a study assessing the effects of pembrolizumab acting as an PD1 inhibitor, with or without concomitant radiotherapy, did not demonstrate any significant tumor response (120). A clinical trial of pembrolizumab with or without radiotherapy showed that 65% of patients achieved disease stabilization for an average of 11 months, but no objective responses were recorded. In a study by Mosconi *et al* (121), no expression of PD-1 or PD-L1 was detected in ACC samples. These findings were corroborated by similar results in a study conducted by Guazzo *et al* (122). By contrast, the high expression level of PD-L2 in ACC tissue has garnered increasing interest in the research field (123,124). In a clinical trial of ACC patients, the PD-1 antibody BGB-A317, which acts as an inhibitor of

both PD-L1 and PD-L2, was combined with the Tet-MYB vaccine (125). It appears that the PD-L1 inhibitors enhance the antitumor effect by restoring T-cell activity and improving the immune system's ability to recognize and attack tumor cells (126).

Vaccines. In the realm of immunomodulatory therapies, the TeTMYB vaccine has been developed to target MYB. This vaccine was constructed using a full-length MYB complementary DNA bound by two potent CD4⁺ epitopes derived from the tetanus toxin, which was subsequently cloned into the complementary DNA vaccine vector pVAX1 (127). Previously, the TeTMYB vaccine demonstrated efficacy in targeting MYB-expressing colorectal cancer in experimental animal studies (127). Subsequently, the TeTMYB vaccine underwent a phase I clinical trial not only for colorectal cancer, but also for salivary gland ACC (125).

Protein arginine methyltransferase 5 (PRMT5). The PRMT5 inhibitor, targets PRMT5, an enzyme responsible for the methylation of arginine residues that serves a significant role in various cellular processes, including cell cycle control, DNA repair or signal transduction (128). However, its role has also been linked to the pathogenesis of several types of cancer, including ACC (129). The involvement of PRMT5 in cancer is primarily due to its inhibition of tumor suppressor gene expression, leading to a loss of control over carcinogenesis (130). In a phase I clinical trial involving 14 patients with ACC, the PRMT5 inhibitor GSK3326595 demonstrated a partial response rate of 21% (3 out of 14 patients) (130). Another study evaluating the PRMT inhibitor PRT543 in patients with recurrent or metastatic ACC reported a median progression-free survival time of 5.9 months. With 56 patients participating, the overall response rate was 2% and disease stabilization was observed in 7% of cases (131).

Tropomyosin receptor A (TRKA). The TRK family, a group of receptor tyrosine kinases encoded by NTRK genes, plays a crucial role in the development and proper functioning of the nervous system. TRKA, along with nerve growth factor, is associated with PNI, a phenomenon highly characteristic of ACC and responsible for late recurrences or distant metastases (132). A phase-I clinical trial is assessing the effectiveness of a small molecule, VMD-928, which acts as a TRKA inhibitor, in solid tumors including ACC; however, the results of this trial are yet to be published (133).

Prostate-specific membrane antigen (PSMA). PSMA expression is characteristic not only of prostate cancer cells, but also for other malignant diseases, including salivary ACC (134). Under normal conditions, PSMA may be present on the surface of serous and mucous acinar cells, as well as intercalated and striated duct cells (135). Moreover, PSMA appears to be more densely distributed in the major salivary glands than in the minor salivary glands, as evidenced by the increased uptake of PSMA-ligand on diagnostic images in major salivary glands (136). A study by Klein Nulent *et al* (135) found that PSMA expression was observed in 94% of primary ACC cases, 80% of recurrent tumors and 90% of metastatic tumors. In ACC, PSMA is predominantly localized on

the surface of cancer cells, which has driven research into PSMA-based theranostics (135). A phase II study conducted by van Boxtel *et al* (137) using ⁶⁸Ga-PSMA PET demonstrated PSMA ligand uptake in 93% of patients with ACC. These findings led to the initiation of a phase II trial focusing on PSMA radionuclide therapy (138). Given these results, PSMA expression in ACC could serve as a potential diagnostic marker and open new avenues for innovative therapeutic approaches in the future.

Serine/threonine kinase AKT. AKT serves a pivotal role in various signaling pathways and is often dysregulated in numerous types of human cancer (139). In a study involving patients with advanced stage incurable ACC, the use of MK-2206, an allosteric inhibitor of AKT, yielded no confirmed responses (140). Of the 14 included patients, 13 patients had stable disease, while 1 patient developed disease progression. The median progression-free survival time was 9.7 months, and the median overall survival time was 18.0 months (140). Consequently, AKT inhibition by MK-2206 failed to produce a significant clinical response in patients with ACC. Additionally, in lung cancer, the activation of AKT, which inhibits transcription-dependent mechanisms of ATRA, promotes invasion and cell survival, leading to resistance against retinoic acid treatment (141). This implies that AKT could be a potential therapeutic target not only in lung cancer but also in ACC.

Cancer stem cells (CSCs). Given the high recurrence rates and chemoresistance of ACC, treatments targeting CSCs, which function as tumor-initiating cells and drive chemoresistance, may hold potential in ACC treatment (142). Although CSCs make up ~5% of all tumor cells, they are responsible for tumor heterogeneity and the capacity for self-renewal, making them a potential target for ACC management (143). Therefore, inhibitors targeting CSCs might lead to tumor regression, typically in combination with cytotoxic therapies aimed at simultaneously reducing tumor mass. Therefore, eliminating CSCs could also help reduce recurrence rates, as these cells drive ongoing tumor renewal (144). In a preclinical PDX model of ACC, inhibiting the interaction of MDM2-p53 with a small molecule inhibitor reduced the number of CSCs and increased sensitivity to cisplatin (145). Moreover, after neoadjuvant administration of MI773 and subsequent tumor resection in a preclinical study, no recurrence was observed compared with the control group that were treated with surgical tumor removal alone (107). A preclinical study on vorinostat, a histone deacetylase inhibitor, also demonstrated a reduction in CSCs in ACC (146). Additionally, the combination of vorinostat with cisplatin showed a decreased number of CSCs, indicating its potential to sensitize ACC cells to cisplatin (147). However, in a clinical trial with vorinostat and patients with recurrent/metastatic ACC, only 2 patients had a partial response, while 27 exhibited stable disease (147). A phase II clinical trial assessing the combination of chidamide and cisplatin is currently ongoing (69). In another study that focused on stemness inhibition assessing amcasertib (BBI503), which acts as multiple serine-threonine kinases inhibitor, the disease control rate was assessed at 86%, with 79% alive in the first year of survival since diagnosis (12).

3. Future directions

CDKs. The expression of CDK6 is significantly elevated in ACC samples, measuring 4-fold higher by mass spectrometry compared with that in squamous cell carcinoma (SCC) samples, and 3-fold higher at the mRNA level (148). Furthermore, the expression of the p16 protein, which inhibits CDK6, was observed to be notably lower in ACC samples compared with that in SCC samples (148). Since cyclins and CDKs are key regulators of the cell cycle, with CDK6 inactivating the retinoblastoma protein that acts as a G₁ phase cell cycle inhibitor (149), these findings suggest that CDK6 may serve a key role in the pathogenesis of ACC and therefore, could be considered as a potential therapeutic target for future investigation.

C-X-C chemokine receptor type 4 (CXCR4). Chemokines serve important roles in both innate and adaptive immunity (150). CXCR4 is commonly expressed on numerous types of cancer cells, with its ligand, CXCL12, contributing to cancer progression by promoting cell proliferation, migration and metastasis (151). Under normal conditions, CXCL4 is found on the surface of mesenchymal stromal cells in the lungs, liver, lymph nodes, bone marrow and peripheral nerves (152). In a study conducted by Nulent *et al* (152), CXCR4 expression was observed in 81% of ACC samples. Currently available literature provides data on a number of CXCR4 antagonists, including inhibitors, antibodies and microRNAs, which have been developed to target CXCR4 (153). Nevertheless, CXCR4 antagonists have been found to have limited success in clinical trials due to cellular toxicity, and poor stability and efficacy (153). Moreover, in one study, CXCL12/CXCR4 expression was found to potentially promote PNI by inducing tumor cell differentiation into Schwann-like cells via the Twist/S100A4 axis in salivary ACC (153). However, there are currently no clinical trials assessing the efficacy of these agents in patients with ACC.

4. Conclusions

ACC is a rare malignancy with an indolent course and elusive pathology. Currently available treatment options exhibit limited effectiveness, as late local recurrence or distant metastasis occur in >40% of patients diagnosed with ACC. Despite numerous studies conducted thus far, a definitive therapeutic target effective in ACC treatment has yet to be identified. Furthermore, even various approaches aimed at targeting both specific genes or lymphocytic infiltration in the tumor microenvironment have shown limited success. Despite these advancements, the present review confirms that progress has been made in the search for a standard therapy for ACC, though significant challenges remain. The resistance of ACC to both past and currently tested treatment options underscores the need for further research. Furthermore, the data presented in the current review suggests that multimodal therapies might be more effective in eliciting a response in ACC compared with single-agent treatments. Limited information exists on ACC pathogenesis, partly due to previous studies that repeatedly used contaminated cell lines. It seems that tumor heterogeneity and robust immune evasion mechanisms appear

to contribute to the failure of novel therapies that have been effective in other types of cancer. Consequently, considerable effort must be devoted to identifying molecular causes of ACC and potential therapeutic agents.

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Authors' contribution

KS, AGo, AGa were responsible for conceptualization and methodology. MD, MP and JZ performed software analysis. AGo performed data visualization and investigation. KS wrote the original draft of the manuscript. AGa and KB contributed to the conception and design of the study in addition to data acquisition, analysis, and interpretation. MD was responsible for supervision and validation. MD, JZ, AGo, MMG and KBP reviewed and edited the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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